REMARKS

Claims 1-14 are pending in the application. Claims 1-13 were rejected under 35 U.S.C. § 101, and claim 14 was rejected under 35 U.S.C. § 103(a). Each of the rejections is addressed as follows.

Rejection under 35 U.S.C. § 101

Claims 1-13 were rejected under § 101 as being drawn to non-statutory subject matter, on the basis that these claims include the phrase "use of." As was suggested by the Examiner, these claims have now been amended to be in the form of method claims. Applicants respectfully submit that these claims, which are now drawn to statutory subject matter, are in condition for allowance.

Rejection under 35 U.S.C. § 103(a)

Claim 14 was rejected under § 103(a) for obviousness over Windholz et al., The Merck Index, 10th Edition, 1983, pp. 723-724, in view of Sauvaire et al., Diabetes 47(2):206-210, 1998. This rejection is based on a conclusion that those of skill in the art would assume that the use of a combination of two anti-diabetic compounds, insulin (as described in the Windholz reference) and the mono-hydroxylated amino acid 4-hydroxyisoleucine (as described in the Sauvaire reference), would result in an additive effect, in the absence of evidence to the contrary. Applicants respectfully traverse this rejection.

In order to support a rejection of a claim as being *prima facie* obvious, a cited reference (or a combination of references) must suggest the claimed invention, as well as provide an

expectation of success. The references cited in this rejection do not meet this standard and, therefore, this rejection should be withdrawn. First, applicants note that neither of the cited references suggests combining the drug described in the reference with any other drug, not to mention the specific drug types required in the present claims. Thus, the references certainly do not suggest the claimed invention.

Moreover, the fact that the drugs can each be used to treat the same condition does not mean that those of skill in the art would conclude that use of the drugs in combination would lead to an additive effect. If it were possible to generalize in this manner, then that would mean that it would be expected that combining multiple drugs that each have a small effect on a condition would cure the condition, provided that a sufficient number of drugs were included in the combination, and this certainly is not true. Although it is not uncommon for drug combinations to be used in the treatment of certain diseases, including diabetes and related conditions, the finding of an additive effect is simply not predictable, based solely on the premise set forth by the Examiner (i.e., that the drugs are used to treat the same disease). Thus, because there is no suggestion of the claimed combination in the art, and because there would not have been an expectation of an additive effect, as asserted by the Examiner, this rejection should be withdrawn.

Although claims 1-13 were not subject to the present obviousness rejection, applicants would like to address these claims in this regard nonetheless, in the event that the Examiner were to apply a similar rejection to amended claims 1-13. These claims are drawn to methods of inducing an insulin sensitizing or insulin mimetic effect in a tissue of a patient by administration of a hydroxylated amino acid, such as 4-hydroxyisoleucine. Use of such amino acids in this

manner had not previously been known or suggested. The Sauvaire paper, for example, only teaches that 4-hydroxyisoleucine acts at the level of the pancreas, from which it stimulates insulin secretion, but provides no evidence that the compound may have an insulin sensitizing or insulin mimetic effect. In contrast to the teachings of Sauvaire, experiments described in the present application show that 4-hydroxyisoleucine activates the insulin receptor and its substrate (IRS-1) *in vivo* (Example 1), lowers insulinemia in an animal model of type II diabetes (Example 4), and inhibits the phosphatase activity of IRS-1 (Example 8). Further, the present application shows that 4-hydroxyisoleucine stimulates phosphoinositol 3-kinase activity in the liver and muscle (Examples 2, 3, 5, and 6), and that this stimulation is specific for the insulin receptor, as tested in contrast to the platelet-derived growth factor (PDGF) receptor (Example 7). These observations, which support the present claims to the use of hydroxylated amino acids such as 4-hydroxyisoleucine to induce insulin sensitizing or insulin mimetic effects, as noted above, are nowhere suggested in the Sauvaire reference or in any other reference of which applicants are aware. Thus, applicants respectfully submit that a rejection of amended claims 1-13 should not be made over the prior art.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: February 1, 2005

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